dimethyl ether by refluxing the free base obtained above with acetic anhydride; this has not been possible. The product obtained had lost a methoxy group. This will be discussed further in a subsequent paper.

The Acetanilide of Dibromo-2-aminoresorcinol Dimethyl Ether Melting at 213–214°.—This was obtained by bromination of the acetanilide or the free base in acetic acid and acetic anhydride as described above. It was repeatedly recrystallized from alcohol and subsequently from benzene, forming fine white needle-like crystals.

Anal. Subs., 0.1039: AgBr, 0.1087. Calcd. for $C_{10}H_{11}O_2NBr_2$: Br, 45.15. Found: Br, 45.52.

The isomeric dibromo derivative melting at 187–188° was obtained by brominating the acetanilide of 2-aminoresorcinol dimethyl ether at the temperature of the steam-bath. It was crystallized from benzene.

Anal. Subs., 0.1104: AgBr, 0.1175. Calcd. for $C_{10}H_{11}NBr_2$: Br, 45.15. Found: Br, 45.30.

Summary

It has been shown that the bromine atom enters the meta position to the amino group in 2-aminoresorcinol dimethyl ether.

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[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES]

DERIVATIVES OF MONO- AND DIAMINOHYDROXYPHENYLARSONIC ACIDS

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The practical significance of 3-amino-4-hydroxyphenylarsonic acid lies in its chemical relationship to such valuable medicinal products as arsphenamine and its derivatives, as well as stovarsol (acetarsone). The first is produced by reduction of 3-amino-4-hydroxyphenylarsonic acid, while the latter is the N-acetyl derivative of the same acid. Recent investigations indicate that 3-amino-4-hydroxyphenylarsonic acid itself is valuable in the treatment of protozoan infections.[1] The purpose of this paper is to describe several new derivatives of the above acid and also of the closely related diaminohydroxyphenylarsonic acid, all of which were synthesized by us in the course of chemotherapeutic research.

Of the halogenated 3-amino-4-hydroxyphenylarsonic acids, the 5-chloro[2] and 5-iodo[3] derivatives are known. We succeeded in preparing 5-bromo-3-amino-4-hydroxyphenylarsonic acid by first brominating the corresponding nitrohydroxyarsonic acid and then reducing the resulting product to the amino derivative. The direct bromination of 3-amino-4-

[1] Levaditi and Navarro-Martin, *Compt. rend. acad. sci.*, **174**, 893 (1922); Fourneau, Navarro-Martin and Mr. and Mrs. Trefouel, *Ann. inst. Pasteur*, **37**, 551 (1923); Petzetakis, *Presse Medicale*, March 7, 1925.

[2] Benda and Schmidt, U. S. Patent 1,595,498 (1926).

[3] Macallum, *J. Chem. Soc.*, 1645 (1926); Maschmann, *Ber.*, 59B, 213 (1926).

hydroxyphenylarsonic acid could not be effected because of the readiness with which the amino acid oxidizes. The bromo-amino product can be obtained in even purer form than its parent amino compound, because it is more stable and crystallizes readily from water in beautiful colorless prisms. We assume that in brominating, as in mercurating, 3-nitro-4-hydroxyphenylarsonic acid the halogen, like mercury, enters position 5 of the benzene ring.[4] Most of the chemical properties and solubilities of 5-bromo-3-amino-4-hydroxylphenylarsonic acid are identical with those of the parent compound (3-amino-4-hydroxyphenylarsonic acid) except that it is soluble in hot water. It reacts with acetic anhydride, forming the corresponding acetyl compound, which is particularly interesting because it is a bromo derivative of the pharmaceutically important 3-acetylamino-4-hydroxyphenylarsonic acid (acetarsone). The halogenated compound, however, is more soluble in water.

3,5-Diamino-4-hydroxyphenylarsonic acid can now be produced with good yields due to improvements in the method of preparation. In a previous article[5] the fact that this compound crystallizes with $^1/_2$ molecule of water was overlooked, so that the analytical results now more closely approximate the theoretical figure. N-acyl derivatives of the 3,5-diamino acid are formed with comparative ease; the formyl compound is obtained at ordinary temperature after twenty-four hours, while the other acyl derivatives result within ten to fifteen minutes. In all cases substitution occurred in both amino groups. Of particular interest is 3,5-di-(chloro-acetylamino)-4-hydroxyphenylarsonic acid; it possesses the property of combining with one molecule of an amine, forming the corresponding mono glycyl derivative of the type formula, $C_6H_2(AsO_3H_2)$-$(OH)(NHCOCH_2Cl)(NHCOCH_2HNR)$. These will be described in a subsequent paper.

3-Acetylamino-4-hydroxyphenylarsonic acid is utilized in therapy as such. We prepared various salts of this acid in order to ascertain whether or not they possess any therapeutic advantages over the parent compound. The alkali salts are soluble in water, while the alkaline earth salts, except that of strontium, are insoluble. They all crystallize with water of crystallization; the only exceptions are the strontium and barium salts.

5-Bromo-3-amino-4-hydroxyphenylarsonic acid, as well as its N-acyl and diacyl derivatives, are not more trypanocidal or spirocheticidal than 3-amino-4-hydroxyphenylarsonic acid itself or its acetyl derivative. The least toxic of all the compounds described in this paper is 3,5-di-(acetylamino)-4-hydroxyphenylarsonic acid. Its maximum tolerated dose for white rats by the intravenous route is 1.4 g. per kilogram of body weight; for rabbits, 0.6 g. per kilo. These figures appear more significant when

[4] Stieglitz, Kharasch and Hanke, THIS JOURNAL, **43**, 1185 (1921).

[5] Raiziss and Gavron, *ibid.*, **43**, 583 (1921).

compared with those obtained for 3-acetylamino-4-hydroxyphenylarsonic acid under the same conditions, *viz.*, 0.3 g. per kilo for rats.

Experimental Part

Salts of 3-Acetylamino-4-hydroxyphenylarsonic Acid.—The lithium salt, $Li_2O_3As\cdot C_6H_3(OH)(NHOCCH_3)\cdot 2H_2O$, is prepared by suspending 1 mole of 3-acetylamino-4-hydroxyphenylarsonic acid in a small volume of water, heating to boiling, gradually adding 2 moles of lithium carbonate and heating until the evolution of carbon dioxide ceases. After filtering and cooling, the filtrate is treated with 10 volumes of acetone and the lithium salt separates out immediately. This is filtered off and washed first with acetone and then ether. It is a colorless, amorphous powder soluble in water, methyl and ethyl alcohols; it is insoluble in acetone or ether.

The calcium and barium salts, $CaO_3As\cdot C_6H_3(OH)(NHOCCH_3)\cdot 2H_2O$ and $BaO_3As\cdot C_6H_3(OH)(NHOCCH_3)$, are prepared like the lithium salt except (1) that the parent arsonic acid is suspended in 50 parts of water, (2) the reaction mixture is boiled for twenty minutes and (3) the salts crystallize out spontaneously from the filtrate when cooled to 15°, without the aid of a precipitant. They are washed successively with water, methyl alcohol and ether, and finally air dried. The calcium salt crystallizes in colorless, highly refractive crystals, while the barium compound exists as colorless needles. They are both soluble in hot water but only sparingly so in cold; they are insoluble in methyl or ethyl alcohol, acetone or ether.

The strontium salt, $SrO_3AsC_6H_3(OH)(NHOCCH_3)$, is prepared like the lithium salt except that it is precipitated from the filtrate at 10° with 3 volumes of 95% methyl alcohol. It is allowed to stand at 10° for one hour, then filtered off and washed first with methyl alcohol and ultimately with ether. It forms colorless rhombohedra which are very soluble in cold water but insoluble in organic solvents.

TABLE I

ANALYTICAL DATA

Salt of	Nitrogen, % Calcd.	Found	Arsenic, % Calcd.	Found
Lithium	4.33	4.48	23.23	23.58
Calcium	4.01	4.05	21.48	21.95
Barium	3.41	3.31	18.29	18.79
Strontium	3.88	4.05	20.79	21.39

Bromo Derivatives of Aryl Arsonic Acids

5-Bromo-3-nitro-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2BrNO_2OH$.—263 g. (1 mole) of 3-nitro-4-hydroxyphenylarsonic acid is suspended in 800 cc. of 95% methyl alcohol, 20 g. of iron added (as a carrier), the flask connected to a reflux condenser and a solution of 160 g. of bromine in 200 cc. of methyl alcohol introduced drop by drop, with frequent shaking. The reaction must not to be permitted to become too violent. After all of the bromine has been added, the reaction mixture is cooled, filtered and the filtrate treated with 10 volumes of water. The yellow bromo derivative precipitates immediately; it is washed with water and then crystallized from the same medium; yield of recrystallized product, 154 g.

5-Bromo-3-nitro-4-hydroxyphenylarsonic acid crystallizes in yellow, microscopic plates which are soluble in hot water, but almost insoluble in cold, sparingly soluble in dilute hydrochloric acid, readily in dilute alkalies, acetone, ethyl or methyl alcohol, insoluble in ether and most other organic solvents. When heated it starts to decompose at about 280°, but remains unmelted at 300°.

Anal. Calcd. for $C_6H_5O_6NAsBr$: N, 4.08; As, 21.93. Found: N, 3.63; As, 21.46.

5-Bromo-3-amino-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2BrNH_2OH$.—Thirty-four and two-tenths g. of the corresponding nitro compound is dissolved in 50 cc. of 4 *N* sodium hydroxide solution, mixed with a solution of 40 g. of magnesium chloride in 300 cc. of water, the whole cooled to $-5°$ and then stirred mechanically. Ninety-five g. of sodium hydrosulfite is now gradually added in the course of two hours, care being taken that the temperature does not rise above 0°. After all of the hydrosulfite has been introduced, the mixture is stirred for another half hour, when the crude bromo-amino compound precipitates. This is filtered off, washed with a small volume of ice water and purified by dissolving in the least amount of 5% hydrochloric acid, rapidly filtering and neutralizing the cooled filtrate with dilute sodium hydroxide solution until faintly acid to Congo Red. After standing for a short time, the product crystallizes out from solution; it is filtered off, washed with water until free of chlorides and sulfates and then recrystallized from hot water to which Nuchar "W" has been added to decolorize; yield, 14 g. It forms colorless prisms which are soluble in hot water, almost insoluble in cold, insoluble in dilute alkali, dilute hydrochloric acid, ethyl and methyl alcohols, insoluble in acetone, ether and most organic solvents.

Anal. Calcd. for $C_6H_7O_4NAsBr$: N, 4.48; As, 24.04; Br, 25.64. Found: N, 4.35; As, 23.67; Br, 25.30.

5-Bromo-3-acetylamino-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2BrOH(NHOCCH_3)$.—This acid was prepared from the preceding amino compound (10.4 g.) by suspending it in water (100 cc.) and chopped ice (200 g.) and acetylating with acetic anhydride (6.9 g.) at reduced temperature. The whole is mechanically stirred for one hour and the resulting precipitate filtered off and purified by dissolving in *N* sodium hydroxide, decolorizing with Nuchar "W," filtering, cooling the filtrate and acidifying slightly with hydrochloric acid, using Congo Red as an indicator; yield, 6 g. It gives colorless prisms which are soluble in water, 10% hydrochloric acid, dilute alkalies, ethyl and methyl alcohols, but insoluble in ether. It darkens at 267–270° but remains unmelted at 300°.

Anal. Calcd. for $C_8H_9O_5NAsBr$: N, 3.95; As, 21.18. Found: N, 3.88; As, 21.19.

N-Acyl Derivatives of 3,5-Diamino-4-hydroxyphenylarsonic Acid

3,5-Diamino-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2(OH)(NH_2)_2 \cdot {}^1/_2H_2O$.—This compound was first described in a German patent.[6] The method of preparation was later modified by Raiziss and Gavron[5] and still further improved by Raiziss and Fisher.[7] It is obtained by reducing 3,5-dinitro-4-hydroxyphenylarsonic acid with sodium hydrosulfite at low temperature, and is purified by dissolving in dilute hydrochloric acid, filtering and neutralizing the filtrate with dilute sodium hydroxide.

Anal. Calcd. for $C_6H_9O_4N_2As \cdot {}^1/_2H_2O$: N, 10.89; As, 29.18; H_2O, 3.50. Found: N, 10.76; As, 29.00; H_2O, 3.10.

3,5-Di-(formylamino)-4-hydroxyphenylarsonic Acid, $H_2O_3As \cdot C_6H_2(OH)(NHOCH)_2$.—A mixture of 10 g. of 3,5-diamino-4-hydroxyphenylarsonic acid and 30 cc. of 85% formic acid is allowed to react at room temperature overnight, then diluted with 300 cc. of water and cooled. The crude diformyl derivative, which precipitates out, is filtered off, washed with water until free from acid, and finally recrystallized from hot water, using Nuchar as a decolorizing agent; yield of recrystallized product, 5 g.

It forms colorless, short, spear-shaped needles which are very sparingly soluble in cold water, soluble in dilute aqueous sodium hydroxide, ethyl or methyl alcohol, in-

[6] German Patent 224,953 (1910).

[7] Raiziss and Fisher, to be published in "Organic Syntheses."

soluble in most other organic solvents, and is decomposed by hydrochloric acid. When heated it starts to decompose rapidly at about 200° but remains unmelted at 275°.

Anal. Calcd. for $C_8H_9O_6N_2As$: N, 9.21; As, 24.67. Found: N, 9.21; As, 24.52.

The sodium salt of this compound was prepared by dissolving it in aqueous sodium hydroxide and precipitating with 10 volumes of ethyl alcohol.

3,5-Di-(acetylamino)-4-hydroxyphenylarsonic acid, $H_2O_3AsC_6H_2(OH)(NHOCCH_3)_2$, prepared according to the method of Raiziss and Gavron[5] and recrystallized from water, using Nuchar as a decolorizer, is obtained in clusters of colorless needles. It is soluble in boiling water, but only sparingly so in cold, soluble in cold dilute aqueous alkalies, insoluble in dilute acids and the usual organic solvents. It darkens at 235–240° but does not melt at 275°.

Anal. Calcd. for $C_{10}H_{13}O_6As$: N, 8.43; As, 22.60. Found: N, 8.09; As, 22.48.

3,5-Di-(propionylamino)-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2(OH)(NHOCCH_2CH_3)_2$.—12.4 g. of 3,5-diamino-4-hydroxyphenylarsonic acid is suspended in 50 cc. of water, 14.3 g. of propionic anhydride added and the whole refluxed for ten minutes. After diluting with 50 cc. of water and cooling, 10 cc. of concentrated hydrochloric acid is added. The resulting precipitate is filtered off, washed several times with 10% hydrochloric acid, then with water until free of chlorine ions and recrystallized from water, using Nuchar to decolorize; yield, 6 g.

The dipropionyl compound crystallizes in long, colorless silky needles, soluble in hot water, sparingly so in cold water, soluble in dilute aqueous alkalies, insoluble in dilute acids or the usual organic solvents except methyl alcohol, in which it is sparingly soluble. When heated it melts at 197–198° to a dark red liquid.

Anal. Calcd. for $C_{12}H_{17}O_6N_2As$: N, 7.78; As, 20.83. Found: N, 7.77; As, 20.53.

3,5-Di-(butyrylamino)-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2(OH)(NHOCCH_2CH_2CH_3)_2$, is prepared from butyric anhydride like the corresponding propionyl compound, except (1) that 5 g. of copper turnings must be added as a catalyst and (2) after cooling the reaction mixture it is not necessary to dilute with water before precipitating with concentrated hydrochloric acid. It crystallizes from hot water in colorless needles, m. p. 177°, soluble in acetone and methyl alcohol; with other solvents it behaves like the preceding compound.

Anal. Calcd. for $C_{14}H_{21}O_6N_2As$: N, 7.21; As, 19.33. Found: N, 7.08; As, 19.57.

3,5-Di-(chloro-acetylamino)-4-hydroxyphenylarsonic Acid, $H_2O_3AsC_6H_2(OH)(NHOCCH_2Cl)_2$.—To a solution of 24.8 g. of 3,5-diamino-4-hydroxyphenylarsonic acid in 200 cc. of *N* sodium hydroxide solution, 22.6 g. of chloro-acetyl chloride is slowly added during fifteen minutes while stirring rapidly. The reaction starts immediately with considerable evolution of heat. The mixture is then cooled, stirred for one-half hour longer and the desired product obtained by the addition of 20 cc. of concentrated hydrochloric acid. It is filtered off, suspended in 10% hydrochloric acid, again filtered and washed, first with 10% hydrochloric acid, then with water until free of chlorine ions. It is finally purified by recrystallizing from 10% acetic acid, using Nuchar to decolorize.

The compound separates as colorless needles, darkening at 200° and melting with decomposition at 210–211°. It is soluble in dilute aqueous alkalies, methyl alcohol and boiling dilute acetic acid, very sparingly so in hot water, practically insoluble in cold water and insoluble in acetone or ether.

Anal. Calcd. for $C_{10}H_{11}O_6N_2AsCl_2$: N, 6.98; As, 18.70. Found: N, 6.77; As, 19.17.

The sodium salts of these 5 acyl derivatives were prepared but not analyzed.

Summary

1. The following compounds have been prepared and described for the first time: (a) The lithium, calcium, barium and strontium salts of 3-acetylamino-4-hydroxyphenylarsonic acid; (b) 5-bromo-3-nitro-4-hydroxyphenylarsonic acid, 5-bromo-3-amino-4-hydroxyphenylarsonic acid and 5-bromo-3-acetylamino-4-hydroxyphenylarsonic acid; (c) 3,5-di-(formylamino)-, 3,5-di-(propionylamino)-, 3,5-di-(butyrylamino)-, 3,5-di-(chloro-acetylamino)-4-hydroxyphenylarsonic acids and their sodium salts.

2. 5-Bromo-3-amino-4-hydroxyphenylarsonic acid is neither more trypanocidal or spirocheticidal than 3-amino-4-hydroxyphenylarsonic acid or its N-acetyl derivative.

3. The least toxic of all the compounds discussed in this paper is 3,5-di-(acetylamino)-4-hydroxyphenylarsonic acid. When injected intravenously into white rats its maximum tolerated dose is 4.6 times greater than that of 3-acetylamino-4-hydroxyphenylarsonic acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, No. 593]

THE SYNTHESIS OF 6-HYDROXYPIPERONYLIC ACID AND INCIDENTAL COMPOUNDS

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Salicylic acid and its derivatives, notably acetyl-salicylic acid (Aspirin), have proved to be of sufficient therapeutic value to justify additional experimental work for the purpose of gaining more light upon the connection between chemical constitution and physiological effect in the group of the *o*-hydroxybenzoic acids.

The experimental work which follows describes the synthesis of 6-hydroxypiperonylic acid, some of its derivatives and incidental products. This particular acid was selected because we failed to find any description of it in the literature, because it is structurally the methylene ether of a dihydroxysalicylic acid and because of the fact that the methylene-dioxy grouping is of frequent occurrence in natural products, including certain of the alkaloids.

The various lines of approach to this goal are sufficiently indicated in the flow diagram. The route via piperonylic acid proved most satisfactory, for reasons set forth in the Experimental Part.

[1] Based upon the Dissertation submitted by Dr. Elder in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University, 1927. An abstract of this paper was read before the Division of the Chemistry of Medicinal Products, at the Richmond Meeting of the American Chemical Society, April, 1927.